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Therapeutic aspects of cutaneous warts

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Abstract: Cutaneous warts are spread directly by contact from infected persons or indirectly from contaminated surfaces or objects, the transmission usually facilitated by minor breaks in the epidermal barrier. Reinfection and autoinoculation are common methods of spread especially in children .Viral warts can be recalcitrant to treatment or recur despite the use of various destructive and immunotherapeutic modalities. No single treatment is completely successful in every patient as the current treatment modalities focus primarily on either destructing and removing visible lesions or inducing a cytotoxic effect against HPV-infected cells instead of killing the virus

Keywords: *cutaneous warts, Therapeutic aspects*

Introduction

Cutaneous warts are spread directly by contact from infected persons or indirectly from contaminated surfaces or objects, the transmission usually facilitated by minor breaks in the epidermal barrier. Reinfection and autoinoculation are common methods of spread especially in children ***(1).***

Clinical presentation of non-genital cutaneous warts is usually determined by the site of lesions. Common warts are the most frequent type of skin warts. Common warts usually appear as single or multiple neoplasms ranging in size from 1 to over 10 mm on exposed areas of the body areas and not under mechanical pressure such as the fingers, hands, elbows, knees, and face. The characteristic clinical picture of common warts consists of grayish brown, exophytic, hyperkeratotic, dome-shaped papules with a rough surface **(2).**

Studies have shown that HPV27, HPV57, HPV2, HPV1, and HPV4 are the most frequent HPV types detected in samples of common warts worldwide. In immunocompromised individuals skin warts occur more frequently and in greater numbers and are more resistant to treatment**.** Previous studies have shown that HPV2, HP27, and HPV57 can also be detected in the most common warts of renal transplant recipients and HIV-positive patients, confirming that the distribution of wart-associated HPV types in skin warts is mainly independent of the host's immune system, whereas the diversity of other cutaneous HPV types tends to be higher in skin warts of immunocompromised patients **(3).**

Although there is no clear definition for recalcitrant warts in literature, it can be defined as warts that fail to respond to therapies after five treatments over 6 months**.** Viral warts can be recalcitrant to treatment or recur despite the use of various destructive and immunotherapeutic modalities. No single treatment is completely successful in every patient as the current treatment modalities focus primarily on either destructing and removing visible lesions or inducing a cytotoxic effect against HPV-infected cells instead of killing the virus **(4).** Most destructive methods demand numerous sessions and carry a substantial risk of scarring and recurrence. Additionally, they have localized effects and no systemic impact. Thus, they are not suitable for patients with distant and multiple warts. These interventions are typically painful, and are frequently linked with variable success, high recurrence **(5).**

Topical and systemic immunotherapy currently play a key role in treating warts due to their non-destructive effect, simplicity of application, and promising results. Other immunotherapeutic alternatives include cell-mediated immunity (CMI) inducers including Candida and mumps antigens, topical contact sensitizers, and a combination of the drugs **(6).**

A. Physical destructive methods

Cryotherapy

It depends on freezing warts with liquid nitrogen to inducing necrosis by direct cell damage, and some believe that it can stimulate the host immune system which induces severe inflammatory reaction. Cryotherapy is an early and widely practiced method for the treatment of warts with success rates ranging from 31 to 52% after three treatment sessions. Common complications in patients treated with cryotherapy are hypopigmentation, infection, pain, blistering, and scar formation with a recurrence rate of about 30% **(7).**

Electrosurgery

It was suggested that the success rate of cryotherapy treatments is like that of electrosurgery. When electrosurgery was used instead of cryotherapy, there was a significant increase in pain, wound infection, and delayed wound healing after four weeks. Electrosurgery is not a viable method for warts on the plantar aspect **(8).**

Curettage and Surgical Excision

These invasive methods are frequently used to treat warts. Remission rates between 65–85 % have been reported, but they may be associated with a high risk of scarring. Regarding plantar warts, it is recommended not to be removed surgically **(9).**

Laser and photodynamic therapy:

Laser systems are methods of energy-based devices used in the treatment of warts include the carbon dioxide laser and Er:YAG laser which causes nonselective thermal tissue destruction, and the pulsed dye which is more selective as it directly damages the wart by coagulating blood vessels and causing intralesional ischemia. The long-pulsed 1064 nm Nd:YAG laser in the treatment of palmoplantar warts targets the dermal blood vessels and destroy them via photothermolysis**.** However, laser method usually requires several sessions, and the clearance rate after one session ranges between 14% and 22% **(10).**

Photodynamic therapy (PDT) uses light energy to excite a photosensitizing agent (usually 5-aminolevulinic acid), leading to production of reactive oxygen species, which exert cytotoxic effects on targeted cells. Various

studies have shown photodynamic therapy to result in clearance rates of 56–94 % in the treatment of recalcitrant warts **(11).**

B-Chemical destructive procedures:

Salicylic acid: Salicylic acid breaks down intercellular cohesions in the stratum corneum, which results in keratolytic effects. By this mechanism, it leads to a reduction in the diseased tissue. It also induces mild irritant effects that induce an immune response **(12).**

Potassium hydroxide (KOH): When compared to salicylic acid therapy, KOH therapy demonstrated a significantly better treatment response and fewer side effects, as well as increased patient satisfaction **(13).**

Monochloroacetic acid: Monochloroacetic acid has caustic effects **(7).**

Topical Formaldehyde as a disinfectant with antibacterial, and antiviral properties by whitening, and removing the epidermis that contains the virus by drying effect that is comparable to formalin. The most common side effects are redness, irritation, and dryness of the skin **(13).**

Cantharidin: Keratinocytes absorb cantharidin, it is a blistering chemical that is present in the oral secretions of oil beetles (Meloidae). It causes acantholysis by activating neutral serine proteases, which disrupts desmosomal connections between epithelial cells **(14).**

Silver nitrate: The best way to cure warts is to use silver nitrate 95% in a solid formulation, which can be obtained through a caustic antiseptic and astringent pen. may result in skin discoloration that is greyish and localized inflammation **(5).**

Vitamin A derivatives: Topical vitamin A acts by affecting keratinocyte growth and keratinization **(15).**

C- Topical Immunotherapy

Topical Contact Sensitizers: Dinitrochlorobenzene (DNCB), Diphencyprone (DCP), Diphenylcyclopropenone (DPCP), Squaric acid dibutylester Squaric acid dibutylester (SADBE)

DNCB is a strong contact allergen and inducer of delayed-type hypersensitivity. It was utilized to treat a variety of skin conditions (alopecia areata, precancerous and malignant skin lesions). DCP is manufactured as dilutions in acetone and sold in brown UV-opaque bottles. DNCB is a less effective and safer contact sensitizer than DCP (**16).**

SADBE is a common topical sensitizer by causing an HPV-infected tissue to undergo a type IV hypersensitivity reaction. Multiple plantar and common warts can be effectively managed with topical immunotherapy with SADBE **(17).**

Imiquimod

Imiquimod is an immune response modulator with antiviral and anticancer properties. It is a FDA-approved synthetic imidazoquinoline derivative used for treating external genital and perianal warts, actinic keratosis, and superficial basal cell carcinomas. It induces the stimulation, synthesis, and release of IFN-α, Il-1, Il-6, and TNF-α. This induces a cell-mediated immunological response through toll-like receptors 7 and/or 8 **(11).** It has been used off-label to treat non-genital cutaneous warts. It works well for treating stubborn plantar, periungual, and subungual warts **(9).**

Sinecatechins (herbal extract of green tea leaves)

Sinecatechins acts as a scavenger of reactive oxygen-free radicals for anogenital warts to receive FDA approval is topical sinecatechins ointment 15% **(18).**

Also, it has an inhibitory effect on transcription factors. Along with other green tea ingredients, it contains eight distinct catechins. Epigallocatechin gallate, which has the maximum biological activity **(18).**

D- Intralesional Immunotherapy

Activated vitamin D3 Analogues (maxacalcitol)

Maxacalcitol has been used to treat palmoplantar keratosis and psoriasis vulgaris. It has some biological effects on epidermal cells, including cell proliferation and differentiation as well as cytokine synthesis. It affects angiogenesis, tumor invasion, and cell death **(19).**

Interferon (α and γ)

Low-molecular-weight glycoprotein interferon-α is produced by various cell types and functions by blocking the growth of tumor and the reproduction of viruses. For the best results, apply IFN-a-2b, an intralesional IFN FDA-approved for genital warts, twice weekly for three weeks. Activated T cells produce IFN-γ, which has a stronger antiproliferative effect than IFN-a and IFN-b. Additionally, it causes macrophages and natural killer cells to become cytotoxic **(20).**

Measles, mumps, and rubella vaccine

The measles, mumps, and rubella vaccine eliminate warts that have been injected and non-injected, with no side effects and a low chance of recurrence. It has been postulated that the primary immunotherapy mechanism is nonspecific inflammatory response to the injected antigens. Flu-like symptoms and injection site soreness are the most frequent side effects **(21).**

Mycobacterium w

Mycobacterium w is created from an unusual, fast-growing, and nonpathogenic Mycobacterium. It is an antigenic agent that triggers the T-cell response and the cytokine (IL-2, IFN-g) production. Fever, discomfort, sterile pustules at the injection site, and paraesthesia in limbs far from the injected warts are possible side effects **(21).**

Bacillus Calmette–Guérin vaccine (BCG) acts via increasing cytokines including interleukin (IL)-1, IL-2, and TNF-a and activating CD4 cells **(22).**

HPV vaccines

HPV vaccines have shown a well-established efficacy in the prevention of diseases caused by HPV such as anogenital warts, cervical, vulvar, vaginal, and anal cancers. There are three types of HPV vaccines available; a bivalent vaccine against HPV 16, 18, a quadrivalent vaccine against HPV 6,11,16,18 and, a nine-valent vaccine against HPV 6, 11, 16,18,31,33,45,52,58. Human papillomavirus L1 vaccines consist of noninfectious virus like particles of the major capsid protein L1. HPV vaccines are associated with strong cellular immune responses and HPV type-specific neutralizing antibodies*.* On the other hand, studies have described the successful use of bivalent and quadrivalent HPV vaccines in the treatment of warts **(23).**

Intralesional Candida albicans antigen

Candida antigen induces a delayed-type hypersensitivity reaction against both the wart tissue and other antigens. To completely remove HPV infection, it also works by producing Th1 cytokines, which stimulate cytotoxic and natural killer cells. This helps with distant and localized warts. Two distinct techniques are employed. The intradermal candida antigen injection in the volar aspect of the forearm to cause a delayed hypersensitivity reaction **(24).**

Patients who have 5 mm in diameter induration and erythema after 48– 72 hours are deemed responders. Another approach omits the intradermal testing step and involves injecting the antigen straight into the largest wart, injected using an insulin syringe. This treatment is continued every two to three weeks until the warts completely disappear, or up to four sessions if there is no improvement. The therapeutic response has been reported to be widely variable approximately range from 34% to 87%, and it isn't identified why some patients respond poorly to treatment **(24).**

The most frequent adverse effects of candida immunotherapy include myalgia, painful purple digit syndrome, fever, and discomfort, erythema, and edema at the injection site **(25).**

F- Systemic Immunotherapy

Cimetidine (H2 receptor blocker)

In cutaneous diseases, it is used in conditions that are characterized by an increase of histamine release as an adjuvant therapy. Additionally, it suppresses T cells by preventing H2 receptors from doing their job. Cimetidine's immunomodulating action stimulates the immune system of individuals with T-cell immunodeficiency, as seen in the case of cutaneous viral infections such as herpes simplex, molluscum contagiosum, epidermodysplasia verruciformis, zoster, and warts, as well as skin cancers such as malignant melanoma **(26).**

Levamisole

Levamisole is an immunomodulator used in extensive viral infections such as warts and molluscum contagiosum. It stimulates phosphodiesterase breakdown of cyclic AMP while inhibiting destruction of cyclic GMP-this appears to correlate with increased chemotactic responsiveness. An increase in adenosine deaminase and a "scavenger" effect on free radicals. It stimulates delayed type hypersensitivity preferentially, involving upregulation of Th1 cells and IL-2, 12, IFN-gamma and downregulation of Th2 cells with a concomitant effect on IL-4,5,10 **(26).**

It is prescribed in a dose of 2.5 mg/kg two to three times weekly. Though it has shown promise in the treatment of warts when combined with cimetidine, it has not proven effective when used alone. Most common side effects are nausea, taste alteration, rash, alopecia, and a flu-like illness. Agranulocytosis is the most dangerous side effect of levamisole **(6).**

Zinc sulfate

Toll-like receptor (TLR)-mediated regulation of zinc homeostasis influences dendritic cell function. It also has specific anti-viral activity; firstly, by cross-linking the double helix of viral DNA, and secondly, by inactivating the viral surface glycoproteins thus interfering with penetration into a susceptible host cell. Each 100 mg capsule of zinc sulfate contains 22.5 mg elemental zinc. Side effects are nausea, vomiting and mild epigastric distress **(27).**

Systemic Retinoids

Retinoids can affect keratinocyte differentiation and proliferation that may inhibit HPV replication and assembly. It also can cause a reduction in the size of cutaneous or genital warts when used as systemic oral therapy (e.g. acitretin, isotretinoin) **(15).**

Hydroxychloroquine

Notable reaction that was temporally connected with hydroxychloroquine treatment The antiviral property of hydroxychloroquine may have a connection to the patient's experience. Also comforting is the lack of recurrence **(28).**

E- Virucidal and antimitotic Agents

Cidofovir

Cidofovir is a potent nucleoside analog with a strong activity against DNA viruses that has demonstrated efficacy in the treatment of warts (topical, intralesional). It should be used with caution due to the possible risk of renal toxicity **(29).**

Acyclovir

Acyclovir is a purine nucleoside analogue, which acts as a selective inhibitor of herpes virus. Higher clearance rates with cidofovir injection can be attributed to the ability of cidofovir to be activated without the need for viral kinases unlike acyclovir that needs both viral and cellular kinases for activation. Although HPV don't encode their own kinases, promising results were obtained with the use of acyclovir **(29).**

Podophyllin and Podophyllotoxin podophyllin is a cytotoxic agent which is commonly used as a treatment for warts. Podophyllotoxin inhibits the formation of microtubules, thus interrupting the cell cycle. It also has an antiviral effect. This therapy is done directly to warts with a cotton swab weekly for four to six weeks or until the lesion is fully healed **(14).**

5-Fluorouracil

By preventing nucleic acid synthesis disruption, both hosts' DNA and viral DNA, the fluorinated pyrimidine antimetabolite fluorouracil functions as an antineoplastic agent. The abnormal skin rapidly proliferating cells have a higher affinity for 5-FU than normal cells, so prevent infected keratinocytes proliferation**.** It may result in bullae, moderate to severe pain, and onycholysis, or nail detachment (particularly when used for warts close to the nails) **(30).**

Bleomycin is an antibiotic medication developed from Streptomyces verticillus, that has antiviral, anticancer, and pyrimidine and purine base elimination because of its capacity to bond with DNA and cause strand scission. Bleomycin is considered as third line therapy, especially encouraged for recalcitrant warts to conventional methods **(30).**

Bleomycin has been favorably used to treat various skin conditions (hemangiomas, vascular malformations, telangiectasias, several types of cutaneous malignancies, condyloma acuminate, Keloids and hypertrophic scars and the lesions of leishmaniasis cutis). Bleomycin is Food and Drug Administration–approved to treat squamous cell carcinoma (SCC) and lymphoma. Bleomycin injection is indicated in SCC of the head and neck, skin, penis, cervix and vulva. Bleomycin is a cytotoxic antibiotic that is used as an anticancer agent, especially for solid tumors e.g.: testicular and germ cell cancers, Hodgkin lymphomas **(31).**

Mechanism of Action

1. Bleomycin produces DNA strand scission by interacting with O2 and Fe2+ to produce activated species of oxygen. Bleomycin binds to DNA through its amino-terminal peptide and the activated complex generates free radicals**.** It causes single- and double-stranded breaks in DNA. These reactive oxygen species also induce lipid peroxidation, carbohydrate oxidation, and alterations in prostaglandin synthesis and degradation **(32).**
2. Bleomycin affects papovavirus DNA, and when locally injected, its destructive capacity is augmented by hemorrhagic necrosis secondary to microthrombosis **(32).**
3. Studies in vitro indicate that accumulation of bleomycin in cells in the G2 lead to chromosomal aberrations including chromatid breaks, gaps, and fragments, as well as translocations **(33).**
4. Other passible mechanisms underlying the efficacy of bleomycin are the induction of tumor necrosis factor (TNF α), and the appearance of apoptotic cells in warts. It causes acute tissue necrosis that may stimulate an immune response **(33).**
5. Effects of Bleomycin on Cells

❖**Immunocytes:** Bleomycin accumulates in immunocytes such as lymphocytes, macrophages, and neutrophils. Neutrophils cause tissue injury by releasing proteases and active oxygen radicals **(34).**

❖ **Fibroblasts:** In vitro, bleomycin upregulates mRNA expression of extracellular matrix proteins in dermal fibroblasts. Collagen newly synthesized by bleomycin treated fibroblasts is rapidly degraded, suggesting the remodeling process. Also, bleomycin enhances mRNA expression for TGF-b and connective tissue growth factor in skin fibroblasts. Both are fibrogenic cytokines and play an important role in tissue fibrosis**(34).**

❖ **Endothelial Cells** play an important role in the inflammatory response. Bleomycin stimulates E-selectin expression in endothelial cells. Endothelial damage by bleomycin may result in cutaneous changes with vascular involvement. Stimulation of endothelial cells by bleomycin upregulates TGF-b production. Th2-cytokine signaling has a pathogenic role that includes excessive migration and protease activity involved in severe fibrotic lung disease. Intralesional bleomycin has been used for the treatment of warts since the 1970s. Numerous reports have been published on the use of intralesional bleomycin for the treatment of recalcitrant warts with cure rates ranging from 14 to 99% **(35)**.

Intralesional bleomycin was found to be very effective in treating warts particularly in periungual and palmoplantar areas. Bleomycin application was mostly done by drug injection into the lesion through syringes, but other methods such as the use of a dermojet, and prick method can also be applied. Different concentration techniques of bleomycin were used ranging from 0.1 U/mL and up to 3 U/mL **(35)**.

Bleomycin is generally administered intralesionally for dermatologic indications, and doses do not exceed 0.1–2 ml/session monthly with up to 4 injections/wart for warts **(34).**

Cutaneous toxicity usually occurs at total doses of between 200 and 300 units while pulmonary fibrosis occurs at high doses (>450 units) as in cancer chemotherapy**.** Significant dermatologic toxicities in systemic route in cancer chemotherapy including scratch dermatitis, Raynaud's phenomenon, hyperpigmentation, fibrosis, gangrene, alopecia areata, neutrophilic eccrine hidradenitis, edema and nail changes may occur. For a very low dose (1 mg/mL), no systemic side effects have been observed **(36).**

Regarding side effects, injection pain is the most reported, typically lasting 24 to 72 hours. Less commonly reported side effects include eschar formation, localized urticaria, flagellate hyperpigmentation, nail loss and Raynaud's phenomenon and bulla formation. No systemic reactions have been associated with intralesional bleomycin for warts **(36).**

The large variability of cure rates is due to poor bleomycin infiltration and lack of full coverage of large areas. A novel minimally invasive method of combining microneedling with spraying of bleomycin and occlusion had a higher clearance and proved less painful as opposed to bleomycin injection. An advantage of this technique is that it creates transient, aqueous pores in the outermost layer of the skin that can fortify the drug delivery and decrease pain and side effects **(36).**

G- Microwave Therapy Most long-standing plantar warts disappear after three to four sessions of carefully heated, keratinized skin treated with microwave therapy with no post-treatment recovery period and considerable pain during the application **(37).**

H- Autoimplantation therapy: The modified technique of autoimplantation using the pared stratum corneum tissue of the wart instead of the subcutis deep wart tissue for autografting is a safe, efficacious, less traumatic and rapid procedure for the treatment of multiple, recurrent and palmoplantar warts **(37).**

I- Acupuncture

It modulates the immune system and provides acupuncture-like analgesic effects. That might work well in immune-related conditions, such as immunodeficiency syndromes, autoimmune illnesses, infections, and allergy disorders **(38)**.

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